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HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

Cancer Causes Control. 2014 December ; 25(12): 1725–1731. doi:10.1007/s10552-014-0463-6.

Menstrual pain and epithelial ovarian cancer risk

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Abstract

Purpose—Menstrual pain is associated with increased production of inflammatory molecules, such as prostaglandins. Inflammation is involved in pathogenesis of several cancers, including ovarian cancer. In this study we examined the association between menstrual pain and risk of ovarian cancer.

Methods—We conducted a case-control study with 2028 cases of epithelial ovarian cancer, and 2091 age and study center matched controls. Women were asked to report the severity of menstrual pain during their 20s and 30s, when not using oral contraceptives or breastfeeding. We used unconditional logistic regression to evaluate the association between menstrual pain and epithelial ovarian cancer risk overall, and polytomous logistic regression to evaluate whether the association differed across tumor subtypes.

Results—Risk of ovarian cancer was increased in women with moderate (OR=1.22, 95% CI: 1.05–1.42) and severe pain (OR = 1.34, 95% CI: 1.09–1.65) compared to women with no or mild pain during menstrual period. The association differed by histologic subtypes, with significant associations for severe pain with endometrioid (OR = 1.64, 95% CI: 1.15–2.34) and clear cell tumors (OR = 1.91, 95% CI: 1.11–3.28).

Conclusions—Our data suggest that moderate and severe pain during menstrual period is associated with increased risk of epithelial ovarian cancer. Due to high prevalence of menstrual pain in women of reproductive age this observation warrants further studies.

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Conflict of interest: The authors declare that they have no conflict of interest.

Keywords

Ovarian cancer; menstrual pain; endometriosis; histology

Introduction

Ovarian cancer is the most lethal of all gynecological cancers [1]; however the etiology is poorly understood. While repeated damage and repair associated with ovulation, excessive gonadotropin levels, or elevated androgen and progesterone explain some risk factor associations (e.g., parity, oral contraceptive (OC) use)[2–4], other known risk factors such as tubal ligation, endometriosis, and use of genital powder [5–9] likely act through other pathways such as inflammation [10].

Menstrual pain (dysmenorrhea) is a dull, cramping pain of varying intensity in the lower abdomen or pelvis [11], likely is caused by inflammatory processes. While secondary dysmenorrhea can be a consequence of pathological conditions such as endometriosis or pelvic inflammatory disease, primary dysmenorrhea occurs in the absence of known pathological conditions [12] and is thought to be caused by prostaglandins synthesized before menstruation, leading to increased uterine contractility and pain [13–17]. Higher levels of leukotrienes in dysmenorrheic women also may exacerbate uterine contractions [16, 18, 19]. Prostaglandins and leukotrienes are potent mediators of inflammation, and are involved in etiology of many diseases, including some cancers [20–24].

Previously, we observed a non-significant increase in risk with moderate or severe pain in 563 cases and 523 controls [25] in the New England case control study. Here we extend this analysis in greater detail with over 2000 cases to assess the potential association between menstrual pain and ovarian cancer, and we consider the associations by tumor characteristics.

Methods

Study population

Enrollment of cases and controls, including selection criteria and participation rates, in the New England case-control (NECC) study has been described previously [26, 27]. NECC occurred in five phases between 1978 and 2008; data from the first two phases were excluded from this analysis since information about menstrual pain was either not available or was assessed in a way not comparable with subsequent phases. Phases included in this study were NECC3 (1992–1997), NECC4 (1998–2003) and NECC5 (2003–2008). During these phases, 3957 cases were recruited in Eastern Massachusetts and New Hampshire through statewide registries and tumor boards. Of these cases, 3083 (78%) met eligibility criteria and 2203 (71%) were enrolled; this analysis is restricted to 2041 cases with epithelial tumors, excluding mixed mesothelial tumors. In NECC3, 420 (72%) eligible controls identified through random-digit dialing agreed to participate, while 102 (51%) controls identified from town resident lists participated. In NECC4 and NECC5, out of 4366 potential controls identified through drivers' license list (NH) and town residents list (MA),

2940 (67%) were eligible and 1578 (54%) agreed to participate. Controls were frequency matched to the cases based on age and the state of residence. For this analysis we excluded 22 women (13 cases and 9 controls) with missing information on menstrual pain, leading to a final number of 2028 cases and 2091 controls. Study participants underwent in-person interviews where detailed information was obtained on their lifestyle and reproductive factors, body size, medical history and family history of ovarian and breast cancer. This study was approved by the Institutional Review Board at Brigham and Women's Hospital (Boston, MA) and the Geisel School of Medicine at Dartmouth (Hanover, NH). All participants provided an informed consent.

Assessment of exposure, outcome and covariates

Participants were asked to describe menstrual pain during their 20s and 30s when not using birth control pills (NECC3), or in their 20s and 30s when not pregnant, breastfeeding or using birth control pills (NECC4 and NECC5). They could choose among four options: no pain, mild cramps with medication seldom needed, moderate cramps with medications usually needed, and severe cramps with medications and bed-rest required. Women with no or mild pain were grouped and used as reference category.

Information on tumor histologic subtype was obtained from pathology reports and reviewed by a gynecological pathologist. Tumors were classified by behavior (borderline or invasive) and histology (serous, mucinous, endometrioid and clear cell). The following covariates were assessed and used in the analysis: age (continuous), age at menarche (continuous), age at menopause (continuous), duration of breastfeeding (continuous), age at first birth (continuous), age at first pregnancy (continuous), study center (Massachusetts or New Hampshire), history of tubal ligation (yes or no), genital powder use (yes or no), parity (0, 1, 2, 3, 4 or more live born children), history of oral contraceptive (OC) use (< 3 months, 3 months – 1 year, > 1 – 5 years, > 5 years), family history of ovarian and/or breast cancer (yes or no), infertility (yes or no), BMI (<23, 23–25, >25–30, >30), menopausal status (pre or post), and endometriosis (yes or no). Information on endometriosis was obtained from questions about a history of endometriosis, infertility due to endometriosis and reason for hysterectomy (all phases), reason for ovarian surgery (NECC4, NECC5), and reason for pelvic surgery (NECC5). The use of non-steroidal anti-inflammatory drugs (NSAIDs) for menstrual pain was assessed in NECC4 and NECC5, and classified as "yes" if participant reported usually taking prescription or over-the counter pain relievers containing aspirin or ibuprofen for menstrual pain or any other menstrual symptoms.

Data analysis

Unconditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for association between menstrual pain and ovarian cancer risk. In the multivariate model we adjusted for matching factors (age, study center) and known ovarian cancer risk factors (OC use, parity, tubal ligation and family history of ovarian or breast cancer). We then evaluated other potential confounders by adding them individually to the multivariate model (endometriosis, NSAID use, age at menarche, age at menopause, duration of breastfeeding, age at first birth, age at first pregnancy, genital

powder use, BMI and menopausal status). Only covariates that changed the association >10% were included in the final multivariate model.

We assessed whether the association was modified by tubal ligation (yes or no), OC use (<3 months and ≥3 months), NSAID use for menstrual pain (yes or no) and menopausal status (pre or postmenopausal). We used likelihood ratio tests to compare models with and without interaction terms to test for interactions.

Polytomous logistic regression (PLR) [28] was used to simultaneously estimate OR and 95% CIs for ovarian cancer risk across tumor subtypes defined by behavior or histology (high-grade serous, low-grade serous, endometrioid, clear cell, mucinous, other). We adjusted for the same covariates in the PLR model as we did in the logistic regression model. In the PLR analysis, we forced covariates to have the same association with ovarian cancer for all histologic subtypes, except for age and parity which were allowed to vary based on previous analyses demonstrating the risk associated with these exposures varies by subtype [29, 30]. To assess heterogeneity across tumor subtypes, we used likelihood ratio test to compare a null model where menstrual pain was constrained to have the same association across case groups, to an alternative model where the association for menstrual pain was allowed to vary.

Logistic regression analysis was performed using SAS v9.3 (SAS Institute, Cary, NC) and polytomous logistic regression using Stata IC/12 (StataCorp, College Station, TX).

Results

The study population included 2028 cases and 2091 controls. Compared to controls, cases were less likely to have a tubal ligation (13.6 vs. 19.9%), more likely to be nulliparous (31.8 vs. 17.7%) and to use genital powder (31.8 vs. 26.5%), and less likely to have used OC for longer than 3 months (52.1 vs. 63.4%) (Table 1). Endometriosis was more common among cases than controls (9.2 vs. 7.9%); similar results were noted for fibroids (17.1 vs. 14.5%) and family history of breast or ovarian cancer (18.2 vs. 15.3%). Cases were more likely to experience moderate (26.6 vs. 22.9%) or severe (12.7 vs. 9.5%) menstrual pain than controls. Among parous women, average duration of breastfeeding was longer among controls (8.6 months) than among cases (5.8 months). In age and center adjusted models, women with moderate pain had a 30% increased risk of ovarian cancer (95% CI: 1.13–1.51), while women with severe menstrual pain had 51% increased risk (95% CI: 1.23–1.84)(Table 2). Similarly, in the multivariate model, we observed a positive association between menstrual pain and ovarian cancer risk (p_{trend} = 0.0007). Moderate pain was associated with 22% increased risk (95% CI: 1.05–1.42) while severe pain was associated with a 34% increase (95% CI: 1.09–1.65) versus women with no/mild pain. Parity was the only confounder that changed the estimate of the association more than 10%. We observed a 14% (95% CI: 0.96–1.35) increase in risk for women with mild/moderate pain in parous, and 63% (95% CI: 1.21–2.21) increase in nulliparous women. For severe pain, there was a 47% (95% CI: 1.15–1.89) increase in parous, and 26% (95% CI: 0.87–1.82) increase in nulliparous women. However, our ability to test for significant effect modification was limited by small number of nulliparous women in our analysis. Additional adjustment for all

the other potential confounders, including endometriosis, did not change the results (data not shown) and therefore they were not included in the model. Results were similar when excluding 563 cases from the previously published analysis [25], with 21% (95% CI: 1.02–1.43) increased risk for ovarian cancer in women with moderate, and 44% increase (95% CI: 1.12–1.86) for women with severe pain. In women who underwent tubal ligation there was no association between menstrual pain and ovarian cancer risk (p for trend = 0.62), while the association was significant for women with no tubal ligation (p for trend < 0.001). However, the difference between two strata was not statistically significant (p-interaction=0.27). We observed no statistically significant differences in associations by OC use, menopausal status at diagnosis, NSAID use for menstrual pain, or number of ovulatory cycles (p-interaction>0.17; data not shown).

Menstrual pain was associated with increased risk of invasive (comparable OR = 1.39, 95% CI: 1.11–1.74), but not borderline cancers (comparable OR=1.19, 95% CI: 0.83–1.71)(p-heterogeneity=0.69). Although not statistically significant (p for heterogeneity=0.37), there was suggestion of different associations across histologic subtypes of invasive ovarian cancer. We observed a statistically significant association for endometrioid (OR, severe vs. no/mild pain = 1.64, 95% CI: 1.15–2.34) and clear cell (comparable OR=1.91, 95% CI: 1.11–3.28) subtypes, but not for serous high-grade (comparable OR = 1.25, 95% CI: 0.96–1.64), serous low-grade (comparable OR = 0.92, 95% CI: 0.27–3.12) or mucinous tumors (comparable OR = 1.77, 95% CI: 0.99–3.18)(Table 2).

The risk estimates were slightly attenuated after adjustment for endometriosis within specific subtypes, including endometrioid (comparable OR=1.49, 95% CI: 1.04–2.14) and clear cell tumors (comparable OR = 1.55, 95% CI: 0.88–2.70), suggesting that endometriosis may explain at least part of the association between menstrual pain and these types of ovarian cancer.

Discussion

In this large case-control study we observed a significantly increased risk of ovarian cancer in women who had moderate or severe menstrual pain in their 20’s and 30’s, compared to those with no/mild pain. In our previous analysis, we did not observe a significant association between menstrual pain and ovarian cancer risk [25], but that analysis was limited to 563 cases. Two studies reported no association between menstrual pain and ovarian cancer, however, these studies were of limited size (112–558 cases) [31, 32]. A study of 1,576 cases in Australia-wide case-control study found a borderline association between painful periods and ovarian cancer, with women reporting often experiencing painful periods having 17% (95% CI: 0.98–1.40) increase in ovarian cancer risk [33]. Several other small studies showed a suggestive association between menstrual pain and ovarian cancer risk but were not adequately adjusted for potential confounders [34–36]. With 2028 cases in the analyses presented here, we had greater power of detecting a modest association.

Menstrual pain can be a consequence of either primary or secondary dysmenorrhea. Endometriosis is a frequent cause of secondary dysmenorrhea [37], and a risk factor for

some ovarian cancer subtypes, particularly endometrioid and clear cell [9, 33, 38]. In our study menstrual pain was associated with overall ovarian cancer, but significant associations were restricted to endometrioid and clear cell ovarian cancer. However, the number of mucinous and low-grade serous cases might have been too small to observe the difference. Adjusting for endometriosis attenuated the association of menstrual pain with the endometrioid and clear cell subtypes, but the relationship for endometrioid subtype remained significant, suggesting an association between menstrual pain and ovarian cancer independent of endometriosis. Since diagnosis of endometriosis is confirmed only by laparoscopy, there likely is some amount of misclassification in self-reported endometriosis [39], leaving the potential for residual confounding and overestimation of the association. We found no confounding by self-reported diagnosis of fibroids, another potential source of secondary dysmenorrhea. We had no information on other conditions leading to secondary dysmenorrhea.

Primary dysmenorrhea is associated with increased levels of inflammation during menstrual bleeding. Prostaglandin levels in menstrual blood are 2–4 fold higher in dysmenorrheic than non-dysmenorrheic women [14, 40, 41]. Some studies suggest that severity of primary dysmenorrhea is proportional to the prostaglandin concentration in menstrual blood [42]. Levels of several other inflammatory molecules such as leukotrienes and platelet-activating factors also have been implicated in dysmenorrhea, and are correlated with both severity and occurrence [16, 19]. High levels of both prostaglandins and leukotrienes reflect high levels of inflammation, and have been observed in several cancers [43–45]. Inflammatory molecules in menstrual blood could reach fallopian tubes and ovaries through retrograde menstruation that occurs in 76–90% of women with unobstructed fallopian tubes [46–48]. They could perhaps act synergistically with inflammation already occurring as a consequence of ovarian epithelium disruption caused by ovulation [49, 50]. Consistent with this hypothesis, menstrual pain was not clearly associated with ovarian cancer risk in women who had tubal ligation that prevents retrograde menstruation, while there was a linear trend in women who had not undergone tubal ligation. However, this difference was not statistically significant, most likely due to a small number of women with both tubal ligation and severe pain.

Due to the retrospective nature of this study, there was potential for recall bias of menstrual pain. However, recall bias would not explain suggestively different association with menstrual pain across histological subtypes. We were not able to separate secondary from primary dysmenorrhea due to a lack of information on conditions leading to secondary dysmenorrhea, other than endometriosis and fibroids which were self-reported. Strengths of our study include its large sample size of invasive epithelial cases and detailed covariate data allowing controlling for potential confounders.

Conclusion

In summary, our results show that compared to no or mild menstrual pain, moderate and severe pain are associated with increased risk of epithelial ovarian cancer, in particular for endometrioid and clear cell tumors. Even though ovarian cancer is a relatively rare malignancy, dysmenorrhea is a highly common complaint, with 16–91% of women of

reproductive age being affected [51]. Therefore, even a modest association would have important public health implications. Further investigation of this association in independent populations and in prospective studies is critical. Together with other known risk factors, it could help identify women who are at high risk that would benefit from more frequent screening.

Acknowledgments

This work was supported by the National Cancer Institute at the National Institutes of Health (R01CA54419, P50CA105009 and 5T32CA009001-38), and the Department of Defense (W81XWH-10-1-0280).

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Table 1

Descriptive characteristics of invasive ovarian cancer cases and controls

Characteristics	Cases (n = 2028)	Controls (n = 2091)
Mean (SD)		
Age (years)	52.5 (12.1)	52.4 (12.5)
Age at menarche (years)	12.6 (1.5)	12.7 (1.6)
Age at menopause (years)	49.3 (5.1)	49.5 (4.8)
Age at first pregnancy[a] (years)	24.6 (4.9)	25.3 (5.1)
Duration of breastfeeding[a] (months)	5.8 (11.5)	8.6 (5.1)
Body mass index (kg/m^2)	26.5 (6.3)	26.1 (5.6)
Study center, n (%)		
Massachusetts	1611 (79.4)	1700 (81.3)
New Hampshire	417 (20.6)	391 (18.7)
History of tubal ligation, n (%)		
no	1753 (86.4)	1673 (80.0)
yes	275(13.6)	418 (19.9)
Parity (number of children), n (%)		
0	644 (31.8)	371 (17.7)
1	290 (14.3)	267 (12.8)
2	536 (26.4)	665 (31.8)
3	320 (15.8)	417 (19.9)
≥4	238 (11.7)	371 (17.7)
Months of oral contraceptives, n (%)		
<3	972 (47.9)	765 (36.6)
3–12	194 (9.6)	160 (7.7)
12–60	466 (22.9)	541 (25.9)
>60	396 (19.5)	625 (29.9)
Menopause, n (%)		
no	889 (43.8)	924 (44.2)
yes	1139 (56.2)	1167 (55.8)
Number of ovulatory cycles[b]**,** n (%)		
<366	733 (36.1)	961 (45.9)
≥366	1135 (56.1)	962 (46.0)
Use of genital powder (%)		
no	1383 (68.2)	1536 (73.5)
yes	645 (31.8)	555 (26.5)
History of endometriosis, n (%)		
no	1841 (90.8)	1926 (92.1)
yes	187 (9.2)	165 (7.9)
Infertility, n (%)		
no	1641 (80.9)	1697 (81.2)

Characteristics	Cases (n = 2028)	Controls (n = 2091)
yes	387 (19.1)	394 (18.8)
Fibroids, n (%)		
no	1681 (82.9)	1787 (85.5)
yes	347 (17.1)	304 (14.5)
Family history of breast or ovarian cancer, n (%)		
no	1659 (81.8)	1770 (84.7)
yes	369 (18.2)	321 (15.3)
Menstrual pain, n (%)		
no pain	451 (22.2)	492 (23.5)
mild	779 (38.4)	922 (44.1)
moderate	540 (26.6)	479 (22.9)
severe	258 (12.7)	198 (9.5)

[a] Among parous women

[b] Percents don’t sum to 100 due to missing observations for 160 cases and 168 controls

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for the association between menstrual pain and overall or histological subtype-specific risk of invasive ovarian cancer.

	Cases N (%)	Controls N (%)	Overall (n=2028) OR (95% CI)[b]	Endometrioid (n = 329) OR (95% CI) [d]	Clear cell (n = 116) OR (95% CI)[d]	Serous high-grade (n = 893) OR (95% CI) [d]	Serous low-grade (n=33) OR (95% CI) [d]	Mucinous invasive (n=92) OR (95% CI)[d]
No or mild pain	1230 (60.7)	1414 (67.6)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Moderate pain	540 (26.6)	479 (22.9)	1.22 (1.05–1.42)	1.37 (1.04–1.81)	1.61 (1.04–2.49)	1.17 (0.96–1.42)	1.04 (0.46–2.36)	0.85 (0.49–1.46)
Severe pain	258 (12.7)	198 (9.5)	1.34 (1.09–1.65)	1.64 (1.15–2.34)	1.91 (1.11–3.28)	1.25 (0.96–1.64)	0.92 (0.27–3.12)	1.77 (0.99–3.18)
P for trend[c]			0.0007	0.002	0.006	0.039	0.947	0.17
								$P_{heterogeneity}$e = 0.37

[a] Participants were frequency matched on age and study center

[b] Adjusted for age, study center, parity, OC use, tubal ligation and family history of ovarian or breast cancer

[c] P-value for trend was obtained using ordinal categories for menstrual pain

[d] Adjusted for age, study center, parity, OC use, tubal ligation and family history of ovarian or breast cancer in the polytomous logistic regression model

[e] P-value for heterogeneity was obtained using likelihood ratio test